I. Remarks

Claims 1-7, 25, and 26 are currently pending.

Claims 1, 4, 5, 7, and 25 have been amended. The amendments to these claims are supported throughout the instant specification and claims. Accordingly, these amendments do not add new matter. Applicants respectfully request their entry.

II. Claim rejections under 35 U.S.C. § 112, second paragraph

Claims 2-7 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 2-6 stand rejected under 35 U.S.C. § 112, second paragraph, because there is allegedly no nexus between the administration of the substance administered and the method objective to identify a putative cancer therapeutic recited in claim 1. Applicants respectfully traverse.

Claim 1 has been amended to delete the phrase "...to identify a putative cancer therapeutic". As such, claims 2-6 particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully request withdrawal of the rejection.

B. Claims 1, 4, and 5 stand rejected under 35 U.S.C. § 112, second paragraph, because the metes and bounds of said claims are allegedly unclear. The Office alleges that it is unclear what the "putative cancer therapeutic" is at the conclusion of each claim. Applicants respectfully traverse.

Claims 4 and 5 have been amended to clarify the metes and bounds of the putative cancer therapeutic effect in each claim. Therefore, claims 1, 4, and 5 do particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully request withdrawal of the rejection.

C. Claims 4, and 5 stand rejected under 35 U.S.C. § 112, second paragraph, because they are vague in the recitation of "determining if said immune effector cells are immunogenic" and "determining if said antibodies are immunogenic". Applicants respectfully traverse.

Claims 4 and 5 do not contain the indicated language. Applicants believe that this rejection was unintentionally repeated from the prior Office Action but respectfully request clarification of the rejection, if it was intentionally maintained.

III. Claim rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 5, and 6 stand rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly does not provide enablement for a method to identify a putative cancer therapeutic that stimulates a humoral response. Applicants respectfully traverse.

The instant claims are drawn to a method of identifying antibodies, which are reactive against a uniquely expressed or over-expressed protein in a target human cancer cell, that have a putative therapeutic effect against said target human cancer. This method is enabled because the skilled artisan could practice step (e) without undue experimentation based on the disclosures of the instant specification and the skill level in the art at the time of the application's filing.

On page 4, second full paragraph of the Office Action, the Office has acknowledged the enablement of steps (a) - (d) of the claimed methods. It is the specific limitation of step (e), which the Office has concluded is not enabled. Applicants assert that step (e) is enabled. This step comprises two parts. First, it requires the administration of the specific antibodies generated in step (d) to a subject. Those of ordinary skill in the art routinely practiced the administration of antibodies to subjects at the time of the instant application's filing. For example, the monoclonal antibody Trastuzumab (tradename Herceptin) had been approved by the FDA as a human drug as of September 25, 1998, which demonstrates the high level of skill in antibody administration present in the art. Second, step (e) requires the measurement of an immune response against the target cancer cell of steps (a) and (c). As stated by the instant specification, methods of determining whether an immune response to the target cancer cell has been induced were also well-known in the art at the time of filing (see paragraph [0059].) Examples of these methods include the routinely practiced FACS analysis and cytotoxic T-lymphocyte assays. Therefore, Applicants assert that the skilled artisan could practice step (e) without undue experimentation. Thus, the instant claims, which are drawn to a method of identifying antibodies that have a putative therapeutic effect against specific target human cancer cells are enabled.

Finally, Applicants respectfully note that the claim 5 as currently amended does not depend on claim 1. Therefore, with respect to claim 1, this rejection no longer applies. Applicants respectfully request withdrawal of the instant rejection for claims 1, 5, and 6.

IV. Claim rejections under 35 U.S.C. § 112, first paragraph

Claims 1 and 2 stand rejected under 35 U.S.C. § 112, first paragraph because they contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and or use the invention. The Office has concluded that the specification is not enabling with respect to the use of *in vivo* gene delivery. Applicants respectfully traverse.

In particular, the Office alleges that 1) the instant specification allegedly fails to teach how to overcome the problems associated with in vivo delivery and expression with respect to the claimed nucleic acids or nucleic acid delivery vehicles and 2) the art of gene therapy and gene delivery is unpredictable. The Office cites a number of references, which discuss the effectiveness and efficiency of in vivo gene therapy for human clinical use. Applicants respectfully point out that the limitations discussed by the Office, e.g. those involved in the clinical use of gene therapy vectors to treat disease in humans, are significantly different than those significantly different than those relevant with respect to the enablement of these gene therapy techniques under 35 U.S.C. § 112. The standard for enablement under 35 U.S.C. § 112 is that one skilled in the art can make and use the invention without undue experimentation.

Claims 1 and 2 comply with the enablement requirement. The reasonably skilled artisan could make and use the claimed invention without undue experimentation based on the disclosures in the specification, the skill level of the artisan at the time of filing, and the state of the prior art at the time of filing.

First, the specification instant provides significant guidance with respect to gene therapy vectors useful in the instant methods. It discloses the production, composition, and use of a number of the major gene therapy vector systems that were widely utilized in the art at the time of filing (see paragraphs [0116] - [0119].) These gene therapy systems include 1) adenoviral vectors (see paragraphs [0125], [0127]); 2) adeno-associated viral vectors (see paragraphs [0125], [0127]); 3) retroviral vectors (see paragraph [0126]), and 4) non-viral vectors including cationic lipid:DNA complexes and plasmids (see paragraphs [0120] - [0124]).

Next, the skill level of the artisan, with respect to administration of a gene delivery vehicle to a subject, was high at the time of filing. Applicants point to the references cited by the Office as a demonstration of this. First, as early as 1995, Orkin et al. reports "the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols." In these trials, more than 597 individuals were treated in gene transfer experiments using vectors such as retrovirus, adenovirus, adeno-associated virus, and cationic liposome complex. (See Orkin et al. at page 1, point 2; page 11, last paragraph; and page 22, Table 2.) Next, the Eck reference cited by the Office does discuss the

limitations to the clinical application of gene therapy but is actually quite positive about the utility of gene therapy. The Eck reference further provides a detailed description of the major gene therapy systems (for example, retrovirus, adenovirus, adeno-associated virus) as well as providing a list of therapeutic gene therapy protocols approved through 1994 (See Eck et al. at Table 5-1.) By 1997, the Verma reference cited by the Office reports that more than 200 clinical trials had been launched in the United States alone (see page 242, column 1, first full paragraph.) This reference also discusses the major gene delivery systems used in the art.

Applicants assert that these three references provide substantial evidence that *in vivo* gene delivery systems were widely known and used by skilled artisans prior to the instant application's filing date. The major gene delivery systems discussed in the instant application are extensively discussed and cited by each reference. More importantly, however, the references demonstrate that gene delivery systems were being administered to human subjects under trials approved by the FDA. Applicants assert that this fact provides further and compelling support that the skilled artisan was able to practice the *in vivo* administration of a gene delivery vehicle to a subject, as required by the instant claims, without undue experimentation. These references make it apparent that the FDA considered the skill in the art sufficient to treat a human patient in vivo. Applicants assert that such a high level of skill also demonstrates that these gene therapy techniques are enabled under 35 U.S.C. § 112. One skilled in the art can make and use the invention without undue experimentation. Therefore, Applicants respectfully request withdrawal of the instant rejection.

V. Claim rejections under 35 U.S.C. § 102(e)

Claims 1, 3, 4, 7, 25, and 26 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Scanlan et al. (U.S. Patent No. 6,686,147). In particular, the Office has concluded that Scanlan anticipates the instant invention based on the references use of the serex method. This conclusion rests on the premise that the serex method allegedly comprises 1) first identifying cancer associated antigens uniquely expressed or over expressed relative to non-cancerous cells and 2) second determining the immunogenicity of the antigens isolated by the first screen, which thus anticipates the claimed invention. Applicants respectfully traverse. Scanlan does not and cannot anticipate the instant invention because the serex method does not first identify a human cancer cell antigen that is uniquely expressed or overexpressed when compared to a human non-cancer control cell. This first step, where the polynucleotide's expression is identified as uniquely expressed or overexpressed as compared to the control cell, is required by the instant invention.

Applicants have enclosed the reference (Sahin et al., 1995, Proc. Natl. Acad. Sci. USA, 92:11810) cited by Scanlan in describing the serex method utilized to identify cancer antigens. Sahin

describes the serex method, which is a process used to identifies tumor associated antigens using the following process. First, cDNA expression libraries are prepared from RNA isolated from fresh tumor biopsies. *E. coli* is transfected with the cDNA expression libraries then immunoscreening using autologous serum to detect antigenic clones is performed. Positive clones are sequenced to identify the antigen. Then, following the establishment of immunogenicity and determination of the antigen sequence, the identified antigen's expression pattern in the tumor is compared to the antigen's expression pattern in normal tissues. (See Sahin et al., Materials and Methods, page 11810 - 1811.) The determination of antigen immunogenicity is performed first, the antigen's sequence identification is performed second, and the antigen's comparison to a non-cancer control cell is performed third in the serex method.

In contrast, the instant claims require that the first step comprises identifying a polynucleotide which is uniquely expressed or overexpressed in a target human cancer cell as compared with a control human non-cancer cell. The second step comprises determining the polynucleotide's protein sequence; the third step comprises determining the identified protein's immunogenicity. Therefore, Scanlan's use of the serex method does not and cannot anticipate the claimed invention. The serex method steps are not performed in the order required by the instant method. As such, Applicants respectfully request that the instant rejection be withdrawn.

VI. Claim Amendments under 37 C.F.R. § 1.121

1. (Currently amended) A method ~~to identify a putative cancer therapeutic~~ comprising the steps and in the order of:

(a) identifying a polynucleotide which is uniquely expressed or overexpressed in a target human cancer cell as compared with a control human non-cancer cell;

(b) determining the protein corresponding to said identified polynucleotide;

(c) determining if said protein, or fragment thereof, is immunogenic, wherein the ability of said protein, or fragment thereof, to elicit an immune response against said target cancer cell is indicative of a putative cancer therapeutic effect by said protein, or fragment thereof.

2. (Previously presented) The method of claim 1, further comprising the step (d) wherein said immunogenic protein, or fragment thereof, is administered to a subject in a gene delivery vehicle.

3. (Previously presented) The method of claim 1, further comprising the step (d) wherein said immunogenic protein, or fragment thereof, is administered to a subject in an antigen presenting cell.

4. (Currently amended) ~~The~~ A method ~~of claim 1, further~~ comprising the steps and in the order of:

(a) identifying a polynucleotide which is uniquely expressed or overexpressed in a target human cancer cell as compared with a control human non-cancer cell;

(b) determining the protein corresponding to said identified polynucleotide;

(c) determining if said protein, or fragment thereof, is immunogenic, wherein the ability of said protein, or fragment thereof, to elicit an immune response against said target cancer cell is indicative of immunogenicity;

(d) generating immune effector cells reactive with an immunogenic protein, and

(e) administering [[if]] said immune effector cells, to a subject wherein the ability of said immune effector cells to elicit an immune response against said target cancer cell is indicative of a putative cancer therapeutic effect by said immune effector cells.

5. (Currently amended) ~~The~~ A method ~~of claim 1, further~~ comprising the steps and in the order of:

(a) identifying a polynucleotide which is uniquely expressed or overexpressed in a target human cancer cell as compared with a control human non-cancer cell;

(b) determining the protein corresponding to said identified polynucleotide;

(c) determining if said protein, or fragment thereof, is immunogenic, wherein the ability of said protein, or fragment thereof, to elicit an immune response against said

target cancer cell is indicative of immunogenicity;

(d) generating antibodies reactive with an immunogenic protein and,

(e) administering [[if]] said antibodies to a subject, wherein the ability of said antibodies to elicit an immune response against said target cancer cell is indicative of a putative cancer therapeutic effect by said antibodies.

6. (Original) The method of claim 5, wherein said antibodies are monoclonal antibodies.

7. (Currently amended) A method to design a cancer vaccine from a sample obtained from a subject suffering from cancer, the improvement comprising:

identifying an amino acid sequence with novel immunogenicity, ~~which is not known to be antigenic, but~~ which is (i) firstly, identified as uniquely expressed or overexpressed in a target human cancer cell from said subject, as compared with a control human non-cancer cell, and (ii) secondly, determined as capable of eliciting an immune response against said target cancer cell; and designing a cancer vaccine corresponding to said amino acid sequence.

8. (Withdrawn) A method for inducing an immune response against a target cell in a subject, comprising delivering to the subject an effective amount of an antigenic peptide that is uniquely expressed or overexpressed in the target cell and has not been previously identified as having the ability to induce an immune response in the subject, whereby an immune response is mounted against the target cell.

9. (Withdrawn) The method of claim 8, wherein the peptide is delivered as a sequence of amino acids.

10. (Withdrawn) The method of claim 8, wherein the peptide is delivered as a polynucleotide that encodes the antigenic peptide.

11. (Withdrawn) The method of claim 8, wherein the uniquely or overexpressed polynucleotide is identified by the method comprising:

(a) obtaining a set of polynucleotides representing gene expression in a target cell;

(b) obtaining a set of polynucleotides representing gene expression in a control cell;

(c) identifying a unique or overexpressed polynucleotide in the target cell as compared to the control cell; and

(d) identifying a unique or overexpressed polynucleotide which is capable of eliciting an immune response in the subject.

12. (Withdrawn) The method of claim 8, further comprising administering an effective amount of a cytokine and/or co-stimulatory molecule to the subject.

13. (Withdrawn) The method of claim 10, wherein the polynucleotide is administered to the subject in a gene delivery vehicle.

14. (Withdrawn) The method of claim 10, wherein the polynucleotide is administered to the subject in a host cell.

15. (Withdrawn) The method of claim 14, wherein the host cell is a antigen presenting cell.

16. (Withdrawn) The method of claim 14 or 15, further comprising administering an effective amount of a cytokine and/or co-stimulatory molecule to the subject.

17. (Withdrawn) A method for enhancing an immune response in a subject against a target cell, comprising administering to the subject an effective amount of an immune effector cell that was raised against an antigenic peptide that is uniquely expressed or overexpressed in the target cell and has not been previously identified as having the
ability to induce an immune response in the subject, whereby an immune response is mounted against the target cell.

18. (Withdrawn) The method of claim 17, wherein the uniquely or overexpressed polynucleotide is identified by the method comprising:

(a) obtaining a set of polynucleotides representing gene expression in a target cell;
(b) obtaining a set of polynucleotides representing gene expression in a control cell;
(c) identifying a unique or overexpressed polynucleotide in the target cell as compared to the control cell; and
(d) identifying a unique or overexpressed polynucleotide which is capable of eliciting an immune response in the subject.

19. (Withdrawn) The method of claim 17, further comprising administering an effective amount of a cytokine and/or co-stimulatory molecule to the subject.

20. (Withdrawn) The method of claim 17, wherein said immune effector cell is a cytotoxic T lymphocyte.

21. (Withdrawn) A method for enhancing an immune response in a subject against a target cell, comprising administering to the subject an effective amount of an antibody that was raised against an antigenic peptide that is uniquely expressed or overexpressed in the target cell and has not been previously identified as having the ability to induce an immune response in the subject, whereby an immune response is mounted against the target cell.

22. (Withdrawn) The method of claim 21, wherein the uniquely or overexpressed polynucleotide is identified by the method comprising:

(a) obtaining a set of polynucleotides representing gene expression in a target cell;
(b) obtaining a set of polynucleotides representing gene expression in a control cell;
(c) identifying a unique or overexpressed polynucleotide in the target cell as compared to the control cell; and
(d) identifying a unique or overexpressed polynucleotide which is capable of eliciting an immune response in the subject.

23. (Withdrawn) The method of claim 21, further comprising administering an effective amount of a cytokine and/or co-stimulatory molecule to the subject.

24. (Withdrawn) The method of claim 21, wherein said antibody is a monoclonal antibody.

25. (Currently amended) A method ~~to identify a putative cancer therapeutic~~ comprising the steps and in the order of:

a) identifying a polynucleotide which is expressed at a higher level in a target human cancer cell as compared with a control human non-cancer cell;
(b) determining the protein corresponding to said identified polynucleotide;
(c) determining if said protein is immunogenic comprising the steps of:
    (i) introducing a gene transfer vector encoding a sequence corresponding to said protein into an antigen presenting cell (APC) under conditions whereby said encoding sequence is expressed by said antigen presenting cell;
    (ii) culturing naive immune effector cells with said antigen presenting cell under conditions whereby said naïve immune effector cells are educated to recognize antigens presented on the surface of said antigen presenting cell in the context of an MHC molecule;

(iii) determining if said educated immune effector cells can lyse said target cancer cell,

wherein the ability of said protein to elicit an immune response against said target cancer cell is indicative of a putative cancer therapeutic effect by said immune effector cells.

26. (Previously presented) The method of claim 25 wherein said antigen presenting cell is a dendritic cell.

VII. Conclusion

No fee is deemed necessary in connection with the filing of this communication. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 07-1074.

Respectfully submitted,

1/14/05
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